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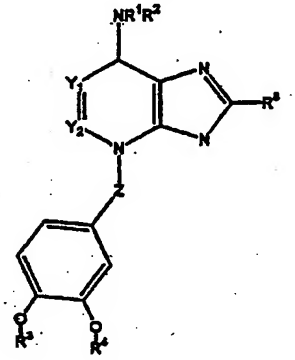
Published
With international search report.

(54) Title: PURINE COMPOUNDS HAVING PDE IV INHIBITORY ACTIVITY AND METHODS OF SYNTHESIS



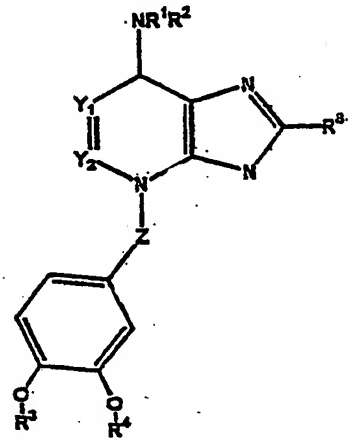
(I)

(57) Abstract

The present invention comprises compounds having general formula (I), wherein: Y_1 is N or CH; Z is selected from the group consisting of alkyl groups such as alkylene groups such as CH_2, CH_2CH_2, $CH(CH_3)$; alkenyl groups such as CH=CH; alkynyl groups such as C≡C; and NH, N(C_1–C_3 alkyl), O, S, $C(O)CH_2$ and OCH_2; R^1 and R^2 are selected from the group consisting of hydrogen and a C_1–C_8 straight or branched alkyl or a C_3–C_8 cycloalkyl; R^3 is a C_1–C_{12} straight or branched alkyl; R^4 is a C_3–C_{10} cycloalkyl optionally substituted with OH or C_3–C_{10} cycloalkenyl optionally substituted with OH; and R^8 is a C_1–C_8 straight or branched alkyl or a C_3–C_8 cycloalkyl, optionally substituted with OH; and methods of synthesis.

Having thus described the invention, what is claimed is:

1. A method of forming a compound having the general formula I



(I)

wherein:

Y_1 is N and Y_2 is selected from the group consisting of N or CH

Z is selected from the group consisting of CH_2;

R^1 and R^2 are independently selected from the group consisting of hydrogen and a C_1 - C_8 straight or branched alkyl or a C_3 - C_8 cycloalkyl;

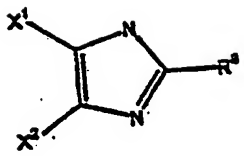
R^3 is a C_1 - C_{12} straight or branched alkyl;

R^4 is a C_3 - C_{10} cycloalkyl optionally substituted with OH, or a C_3-C_{10} cycloalkenyl optionally substituted with OH; and

R^8 is a C_1 - C_8 straight or branched alkyl or a C_3 - C_8 cycloalkyl, optionally substituted with OH;

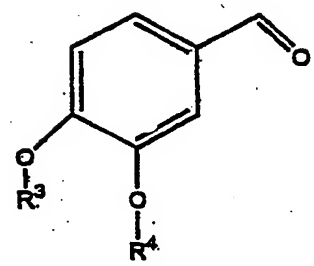
said method comprising the steps of;

(a) reacting a compound of the formula II



(II)

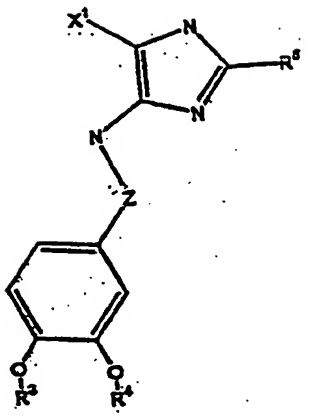
wherein X^1 is a carboxamide and X^2 is an amino group; with the benzaldehyde of compound (III)



(III)

wherein R^3 and R^4 are as defined above ;

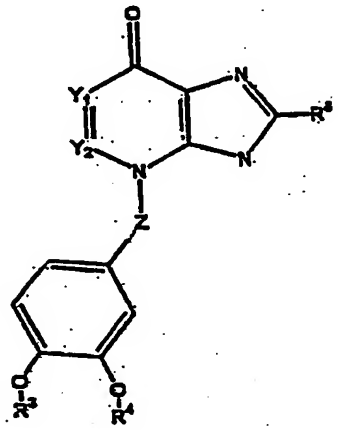
followed by reduction of the resultant compound with a reducing agent to yield compound (IV)



(IV)

wherein Z, X^1, R^3, R^4 and R^8 are as defined above;

(b) reacting compound (IV) to cause cyclization to compound (V) as set forth below



(V)

wherein Y_1, Z, R^3, R^4 and R^8 are as defined above and Y_2 is CH when the cyclization reaction occurs using an ester or Y_2 is N when the cyclization reaction occurs using nitrous acid;

(c) transforming said compound (V) to an amine by successive halogenation and displacement to yield compound (I).

2. The method of claim 1 wherein said reaction with compound (III) occurs in the presence of an acid.

3. The method of claim 2 wherein said acid is selected from the group consisting of tosic acid or p-toluenesulfonic acid.

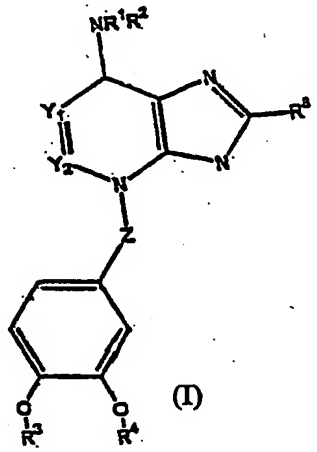
4. The method of claim 1 wherein said reducing agent is a borane anion.

5. The method of claim 1 wherein said ester is triethylorthoformate.

6. The method of claim 1, wherein said halogenating agent is a chlorinating agent.

7. The method of claim 1 wherein said compound of formula I is 3-(3-Cyclopentyloxy-4-methoxybenzyl)-6-ethylamino-8-isopropyl-3H-purine.

8. A method of forming a compound having the general formula I



(I)

wherein:

Y_1 and Y_2 are CH

Z is selected from the group consisting of CH_2;

R^1 and R^2 are independently selected from the group consisting of hydrogen and a C_1 - C_8 straight or branched alkyl or a C_3 - C_8 cycloalkyl;

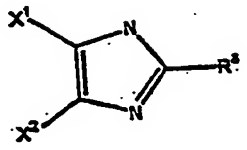
R^3 is a C_1 - C_{12} straight or branched alkyl;

R^4 is a C_3 - C_{10} cycloalkyl optionally substituted with OH, or a C_3-C_{10} cycloalkenyl optionally substituted with OH; and

R^8 is a C_1 - C_8 straight or branched alkyl or a C_3 - C_8 cycloalkyl, optionally substituted with OH;

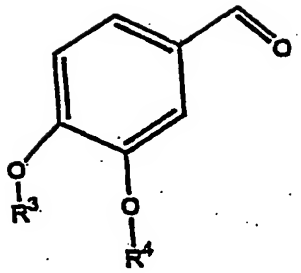
said method comprising the steps of;

(a) reacting a compound of the formula II



(II)

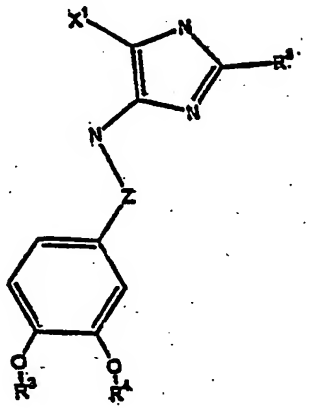
wherein X^1 is a ester and X^2 is an amino group; with the benzaldehyde of compound (III)



(III)

wherein R^3 and R^4 are as defined above ;

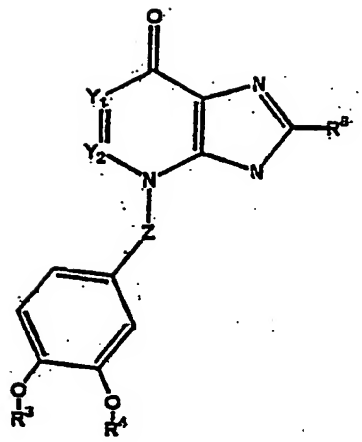
followed by reduction of the resultant compound with a reducing agent to yield compound (IV)



(IV)

wherein Z, X^1, R^3, R^4 and R^8 are as defined above;

(b) reacting compound (IV) with a cyclization agent to yield compound (V) as set forth below



(V)

wherein Y_1, Y_2, Z, R^3, R^4 and R^8 are as defined above

(c) transforming said compound (V) to an amine by successive halogenation and displacement to yield compound (I).

9. The method of claim 8 wherein said reaction with compound (III) occurs in the presence of an acid.

10. The method of claim 9 wherein said acid is selected from the group consisting of tosic acid or p-toluenesulfonic acid.

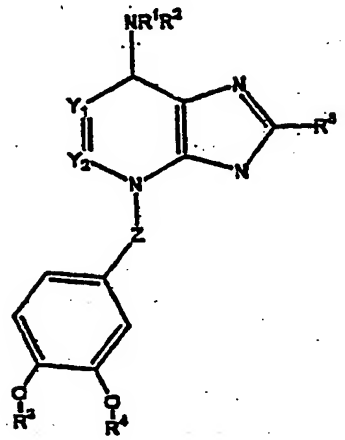
11. The method of claim 8 wherein said ester is ethyl ester.

12. The method of claim 8 wherein said cyclization agent is ethyl 3-ethoxyacrylate.

13. The method of claim 8, wherein said halogenating agent is a chlorinating agent.

14. The method of claim 8 wherein said compound of formula I is 3-(3-Cyclopentyloxy-4-methoxybenzyl)-6-ethylamino-8-isopropyl-3H-purine.

15. A method of forming a compound having the general formula I



(I)

wherein:

Y_1 and Y_2 are CH

Z is selected from the group consisting of CH_2, CH_2CH_2, $CH(CH_3)$, CH=CH, C≡C, NH, $N(C_1 - C_3$ alkyl), O, S, $C(O)CH_2$ and OCH_2;

R^1 and R^2 are independently selected from the group consisting of hydrogen and a C_1 - C_8 straight or branched alkyl or a C_3 - C_8 cycloalkyl;

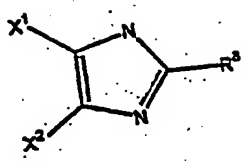
R^3 is a C_1 - C_{12} straight or branched alkyl;

R^4 is a C_3 - C_{10} cycloalkyl optionally substituted with OH, or a C_3-C_{10} cycloalkenyl optionally substituted with OH; and

R^8 is a C_1 - C_8 straight or branched alkyl or a C_3 - C_8 cycloalkyl, optionally substituted with OH;

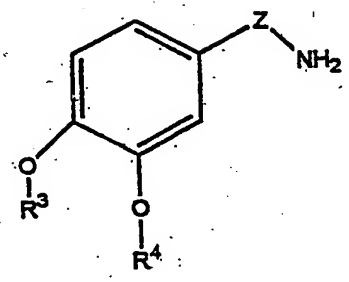
said method comprising the steps of;

(a) reacting a compound of the formula II



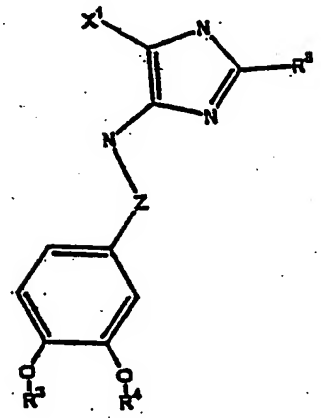
(II)

wherein X^1 and X^2 are halides; with cyanine to remove one halogen, hydrolyzing the resultant nitrile to an ester, and reacting the resultant ester with compound (X)



(X)

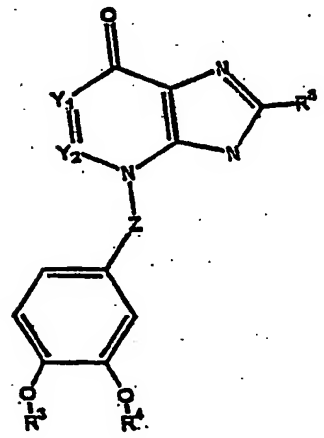
wherein Z, R^3 and R^4 are as defined above , to displace the remaining halogen with the amine, to yield compound (IV)



(IV)

wherein X^1 is an ester and Z, R^3, R^4 and R^8 are as defined above;

(b) reacting compound (IV) with a cyclization agent to yield compound (V) as set forth below



(V)

wherein Y_1, Y_2, Z, R^3, R^4 and R^8 are as defined above

(c) transforming said compound (V) to an amine by successive halogenation and displacement to yield compound (I).

16. The method of claim 15 wherein X^1 and X^2 of compound (II) are bromide.

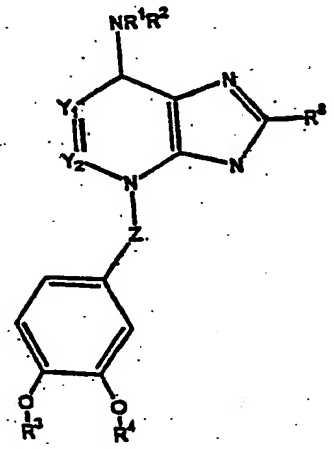
17. The method of claim 15 wherein said cyclization agent is ethyl 3-ethoxyacrylate.

18. The method of claim 15, wherein said halogenating agent is a chlorinating agent.

19. The method of claim 15 wherein said ester of compound (IV) is ethyl ester.

20. The method of claim 15 wherein said compound of formula I is 3-(3-Cyclopentyloxy-4-methoxybenzyl)-6-ethylamino-8-isopropyl-3H-purine.

21. A method of forming a compound having the general formula I



(I)

wherein:

Y_1 and Y_2 are CH

Z is selected from the group consisting of CH_2, CH_2CH_2, $CH(CH_3)$, CH=CH, C≡C, NH, $N(C_1 - C_3$ alkyl), O, S, $C(O)CH_2$ and OCH_2;

R^1 and R^2 are independently selected from the group consisting of hydrogen and a $C_1 - C_8$ straight or branched alkyl or a $C_3 - C_8$ cycloalkyl;

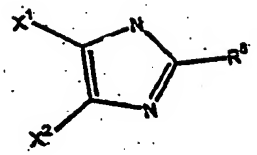
R^3 is a $C_1 - C_{12}$ straight or branched alkyl;

R^4 is a $C_3 - C_{10}$ cycloalkyl optionally substituted with OH, or a C_3-C_{10} cycloalkenyl optionally substituted with OH; and

R^8 is a $C_1 - C_8$ straight or branched alkyl or a $C_3 - C_8$ cycloalkyl, optionally substituted with OH;

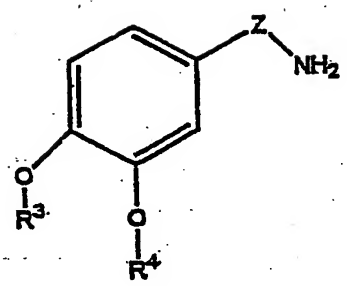
said method comprising the steps of;

(a) reacting a compound of the formula II



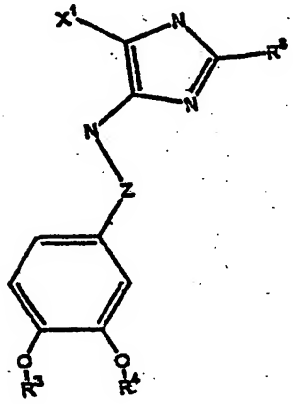
(III)

wherein X^1 and X^2 are halides; with cyanine to remove one halogen, reacting the resultant nitrile to a carboxamide, and reacting the resultant carboxamide with compound (X)



(X)

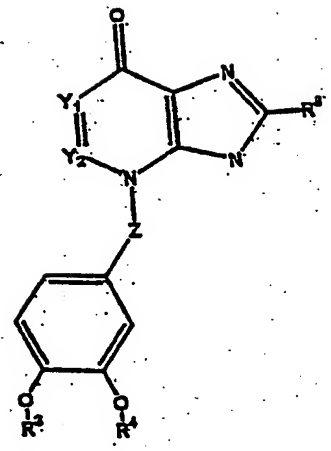
wherein Z, R^3 and R^4 are as defined above, to displace the remaining halogen with the amine, to yield compound (IV)



(IV)

wherein X^1 is a carboxamide and Z, R^3, R^4 and R^8 are as defined above;

(b) reacting compound (IV) to cause cyclization to compound (V) as set forth below



(V)

wherein Y_1, Z, R^3, R^4 and R^8 are as defined above and Y_2 is CH when the cyclization reaction occurs using an ester or Y_2 is N when the cyclization reaction occurs using nitrous acid;

(c) transforming said compound (V) to an amine by successive halogenation and displacement to yield compound (I).

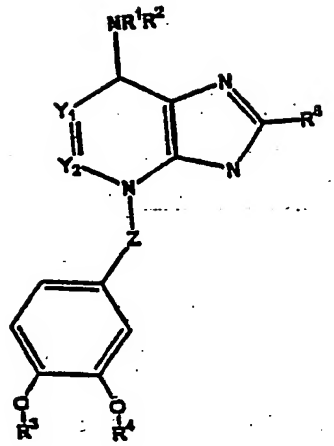
22. The method of claim 21 wherein X^1 and X^2 of compound (II) are bromide.

23. The method of claim 21 wherein said cyclization agent is triethylorthoformate when Y_1 is CH.

24. The method of claim 21, wherein said halogenating agent is a chlorinating agent.

25. The method of claim 15 wherein said compound of formula I is 3-(3-Cyclopentyloxy-4-methoxybenzyl)-6-ethylamino-8-isopropyl-3H-purine.

26. A compound having the general formula (I):



(I)

wherein:

Y_1 and Y_2 are independently selected from the group consisting of CH and N;

Z is selected from the group consisting of CH_2, CH_2CH_2, $CH(CH_3)$, CH=CH, C≡C, NH, $N(C_1 - C_3$ alkyl), O, S, $C(O)CH_2$ and OCH_2;

R^1 and R^2 are independently selected from the group consisting of hydrogen and a C_1 - C_8 straight or branched alkyl or a C_3 - C_8 cycloalkyl;

R^3 is a C_1 - C_{12} straight or branched alkyl;

R^4 is a C_3 - C_{10} cycloalkyl optionally substituted with OH, or a C_3-C_{10} cycloalkenyl optionally substituted with OH; and

R^8 is a C_1 - C_8 straight or branched alkyl or a C_3 - C_8 cycloalkyl, optionally substituted with OH.

27. The compound of claim 26 wherein R^4 is cyclopentyl.

28. The compound of claim 27 wherein R^3 is methyl.

29 The compound of claim 28 where Z is CH_2.

30. A pharmaceutical composition of a compound of claim 26.

31. A method of effecting selective PDE IV inhibition in mammals requiring the same, which comprises administering an effective amount of a compound of claim 26.

32. A method of treating a mammal suffering from a disease state selected from the group consisting of asthma, allergies, inflammation, dementia, atopic diseases, rhinitis, and disease states associated with abnormally high physiological levels of cytokine, comprising administering an effective amount of a compound of claim 26.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/26444

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :C07D 473/34
US CL :544/277
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 544/277

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS Online

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ER-RHAIMINI et al. The photosolvolysis of N-arylmethyl-adenines. Photoremovable N-arylmethyl protective groups for N-containing compounds. Tetrahedron Letters. October 1990, Volume 31 No. 40, pp 5757-57260, see Compound 2.	1-32

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"B"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 22 FEBRUARY 1997	Date of mailing of the international search report 24 MAR 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer MARK L. BERCH SCO Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/26444

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-7 (part), 26-32 (part)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/26444

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

Group I - Compounds & Process where Y_2=CH, Y_1=N
Claims 1-7 (part), 26-32 (part)
Group II - Compounds & Process where Y_2=N, Y_1=N
Claims 1-6 (part) and 26-32 (part)
Group III - Compounds where Y_2=CH, Y_1=CH
Claims 8-13, 15-19, 21-24 and 26-32 (part)
Group IV - Compounds where Y_2=N, Y_1=CH
Claims 26-32 (part)

Claims 14, 20 and 25 are improperly dependent as they are outside the scope of the independent claim from which they depend. However, a search of the compound of claim 7 will also afford a search of claims 14, 20 and 25.

The inventions listed as Groups I, II, III and IV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The description sets forth that the dialkoxy benzyl is well known in the art. Therefore, it cannot constitute a special technical feature within the meaning of PCT 13.2 as it is not a contribution over the art.

Thus, the special technical feature would appear to reside in the heterocycle attached to the dialkoxy benzyl moiety, however, these heterocycles lack a common core as defined below:

Group I: Imidazotriazine
Group II: Purine
Group III: Imidazopyridines
Group IV: Imidazopyridazines.

In addition, these compounds do not belong to a recognized class of chemical compounds.